

FINAL REPORT

Test Facility Study No. 511876

**Assessment of Acute Oral Toxicity with
MLA-3202
in the Rat
(Acute Toxic Class Method)**

SPONSOR:

Chemtura Corporation
199 Benson Road
MIDDLEBURY, CT 06749
USA

TEST FACILITY:

Charles River Laboratories Den Bosch B.V.
Hambakenwetering 7
5231 DD 's-Hertogenbosch
The Netherlands

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2. STATEMENT OF GLP COMPLIANCE

Charles River Den Bosch, 's-Hertogenbosch, The Netherlands

All phases of this study performed by the test facility were conducted in compliance with the following GLP regulations:

- OECD Principles of Good Laboratory Practice concerning Mutual Acceptance of Data in the Assessment of Chemicals, 26 November 1997 (C(97) 186 Final);
- EC Council Directive 2004 (2004/10/EC, February 11, 2004, Official Journal of February 20, 2004).

Except for the following:

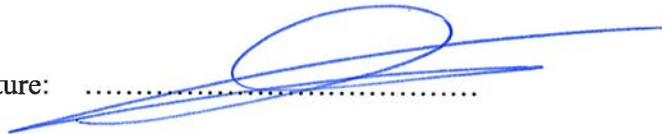
The test item characterisation information supplied by the sponsor was produced under the sponsor's responsibility.

The purity of the test item was unknown, since the test item is a UVCB.

The data generated and reported are considered to be valid.

Charles River Den Bosch

Signature:



Name: A.H.B.M. van Huygevoort, MSc.

Title: Study Director

Date: 15 August 2016

3. TEST FACILITY QUALITY ASSURANCE STATEMENT

Charles River Den Bosch, 's-Hertogenbosch, The Netherlands.

Study title: Assessment of acute oral toxicity with MLA-3202 in the rat (acute toxic class method)

This report was inspected by the Charles River Den Bosch Quality Assurance Unit (QAU) according to the Standard Operating Procedure(s).

The reported method and procedures were found to describe those used and the report reflects the raw data.

During the on-site process inspections, procedures applicable to this type of study were inspected. The dates of Quality Assurance inspections are given below.

Project	511876	Start Inspection date	End Inspection date	Reporting date
Type of Inspections	Phase/Process			
Study	Study Plan	22-Mar-2016	22-Mar-2016	22-Mar-2016
	Report	14-Jun-2016	14-Jun-2016	14-Jun-2016
Process	Test Substance Formulation Test Substance Handling	25-Feb-2016	15-Mar-2016	15-Mar-2016
	Necropsy Observations/Measurements Specimen Handling	01-Mar-2016	11-Mar-2016	14-Mar-2016
	Animal Facilities Test Substance Handling Exposure Observations/Measurements Specimen Handling	04-Apr-2016	15-Apr-2016	15-Apr-2016
	Test Substance Receipt Test Substance Handling	09-May-2016	20-May-2016	24-May-2016

The review of the final report was completed on the date of signing this QA statement.

Charles River Den Bosch

Signature: 

Name: C. Mitchell B.Sc., FRQA
Head of Quality Assurance

Date: 10 Aug 2016

4. SUMMARY

The study was performed to assess the acute oral toxicity of MLA-3202 in the rat (Acute Toxic Class Method). The study was carried out based on the guidelines described in:

- OECD No.423 (2001) "Acute Oral Toxicity, Acute Toxic Class Method"
- Commission Regulation (EC) No 440/2008, B1 tris: "Acute Oral Toxicity, Acute Toxic Class Method"
- EPA, OPPTS 870.1100 (2002), "Acute Oral Toxicity"
- JMAFF Guidelines (2000), including the most recent revisions.

Initially, MLA-3202 was administered by oral gavage to three female Wistar rats at 2000 mg/kg body weight. In a stepwise procedure, one additional group of three females was dosed at 2000 mg/kg, one female at 5000 mg/kg and one group of two females at 5000 mg/kg body weight. Animals were subjected to daily observations and weekly determination of body weight. Macroscopic examination was performed after terminal sacrifice (Day 15).

No mortality occurred.

Hunched posture was seen for all animals on Day 1 and for one animal dosed at 2000 mg/kg on Days 2 and 3 also. Piloerection was seen for the majority of animals on Day 1. Two females dosed at 5000 mg/kg showed abnormal licking on Day 2.

The body weight gain shown by the animals over the study period was considered to be similar to that expected for normal untreated animals of the same age and strain.

Isolated reddish foci on the thymus were found at macroscopic post mortem examination of one female dosed at 2000 mg/kg. No other test item related abnormalities were noted in any of the remaining animals.

The oral LD50 value of MLA-3202 in Wistar rats was established to exceed 5000 mg/kg body weight.

According to the OECD 423 test guideline, the LD50 cut-off value was considered to exceed 5000 mg/kg body weight.

Based on these results, MLA-3202 does not have to be classified and has no obligatory labelling requirement for acute oral toxicity according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) of the United Nations (2015) (including all amendments) and Regulation (EC) No 1272/2008 on classification, labelling and packaging of items and mixtures (including all amendments).

5. INTRODUCTION

Due to the acquisition of WIL Research by Charles River, the name of the WIL Research facility in Den Bosch, has been changed to Charles River Laboratories Den Bosch BV, Hambakenwetering 7, 5231 DD 's-Hertogenbosch, The Netherlands. Study documents may contain both names and both names are considered equivalent and may be used as the name of WIL Research transitions to Charles River.

5.1. Study Schedule

Experimental starting date : 25 March 2016
Experimental completion date : 17 May 2016

5.2. Purpose

The objective of this study was to assess the potential oral acute toxicity of the test item when administered in a single dose to female rats at one or more defined dosages. The design of the study allows the test item to be ranked according to most classification systems currently in use. Since a widespread consumer use was anticipated for the test item, testing for category 5 (5000 mg/kg) was considered appropriate for protecting human health.

This study should provide a rational basis for risk assessment in man. The oral route was selected as it is a possible route of human exposure during manufacture, handling or use of the test item.

5.3. Guidelines

This type of study plan was reviewed and agreed by the Laboratory Animal Welfare Officer and the Ethical Committee (DEC 14-19) as required by the Dutch Act on Animal Experimentation (February 1997). The study procedures described in this report were in compliance with the following guidelines:

- Organization for Economic Co-operation and Development (OECD), OECD Guidelines for Testing of Chemicals, Section 4, Health Effects. No.423, "Acute Oral Toxicity - Acute Toxic Class Method", 2001.
- Commission Regulation (EC) No 440/2008 Part B: Methods for the Determination of Toxicity and other Health Effects; B1 tris: "Acute Oral Toxicity, Acute Toxic Class Method". Official Journal of the European Union No. L142, May 2008, including the most recent amendments.
- United States Environmental Protection Agency (EPA). Health Effects Test Guidelines, OPPTS 870.1100, Acute Oral Toxicity. Office of Prevention, Pesticides and Toxic Items (7101), EPA 712-C-02-190, 2002.
- Japanese Ministry of Agriculture, Forestry and Fisheries (JMAFF), 12 Nousan, Notification No 8147, November 2000; including the most recent partial revisions.

5.4. Retention of Records and Materials

Records and material pertaining to the study, which include study plan and amendments, raw data, specimens, except perishable specimens, and the final report will be retained in the archives of the test facility for a minimum of 5 years after the finalization of the report. After this period, the sponsor will be contacted to determine how the records and materials should be handled. The test facility will retain information concerning decisions made.

A sample of the test item will be retained until expiry date or applicable retest date. After this period the sample(s) will be destroyed.

5.5. Responsible Personnel

5.5.1. Test Facility

Study Director	A.H.B.M. van Huygevoort, MSc.
Coordinating Biotechnician	J.C. van Voorden (Charles River Den Bosch)
Necropsy	M. Schelling (Charles River Den Bosch)
QA	C.J. Mitchell, BSc. (Charles River Den Bosch): christine.mitchell@crl.com
Test Facility Management Representative	H.H. Emmen, MSc. (Charles River Den Bosch): harry.emmen@crl.com

5.5.2. Sponsor Representative

Study Monitor	Audrey Batoon, Ph.D.
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6. MATERIALS AND METHODS

6.1. Test Item

6.1.1. Test Item Information

Test item	207258/A
Identification	MLA-3202
Appearance	Clear amber-red liquid
Batch	RC-1045
Purity/Composition	UVCB
Test item storage	At room temperature
Stable under storage conditions until	17 February 2019 (expiry date)

6.1.2. Study Specific Test Item Information

Purity/composition correction factor	No correction factor required
Test item handling	No specific handling conditions required
Stability at higher temperatures	Stable
Chemical name (IUPAC), synonym or trade name	Amides, tallow, N,N-bis(2-hydroxypropyl)
CAS Number	1454803-04-3
pH	6-7
Specific gravity/density	0.9394

6.2. Test Item Preparation

The test item was dosed undiluted as delivered by the Sponsor.

6.3. Test System

Species	Rat, Wistar strain Crl:WI (Han) (outbred, SPF-Quality). Recognized by international guidelines as the recommended test system (e.g. OECD, EC). Source: Charles River Deutschland, Sulzfeld, Germany.
Number of animals	9 Females (nulliparous and non-pregnant).
Age and body weight	Young adult animals (approx. 8-10 weeks old) were selected. Body weight variation did not exceed +/- 20% of the sex mean.
Identification	Earmark and tail mark
Health inspection	At least prior to dosing. It was ensured that the animals were healthy and without any abnormality that might have affected the study integrity.

6.4. Animal Husbandry

Conditions

Environmental controls for the animal room were set to maintain 18 to 24°C, a relative humidity of 40 to 70%, at least 10 air changes/hour, and a 12-hour light/12-hour dark cycle. Any variations to these conditions were maintained in the raw data and had no effect on the outcome of the study.

Accommodation

Group housing of maximally 3 animals per cage in labeled Makrolon cages (MIV type; height 18 cm.) containing sterilized sawdust as bedding material (Lignocel S 8-15, JRS - J.Rettenmaier & Söhne GmbH + CO. KG, Rosenberg, Germany) and paper as cage-enrichment (Enviro-dri, Wm. Lillico & Son (Wonham Mill Ltd), Surrey, United Kingdom). Acclimatization period was at least 5 days before start of treatment under laboratory conditions.

Diet

Free access to pelleted rodent diet (SM R/M-Z from SSNIFF® Spezialdiäten GmbH, Soest, Germany).

Water

Free access to tap water.

Diet, water, bedding and cage enrichment evaluation for contaminants and/or nutrients was performed according to facility standard procedures. There were no findings that could interfere with the study.

6.5. Study Design

The toxicity of the test item was assessed by stepwise treatment of groups of females. The first group was treated at a dose level of 2000 mg/kg. The absence or presence of mortality of animals dosed at one step determined the next step, based on the test procedure defined in the guidelines. The onset, duration and severity of the signs of toxicity were taken into account for determination of the time interval between the dose groups.

6.6. Treatment

Method	Oral gavage, using plastic feeding tubes. The test item were stirred on a magnetic stirrer during dosing.
Fasting	Animals were deprived of food overnight prior to dosing and until 3-4 hours after administration of the test item. Water was available <i>ad libitum</i> .
Frequency	Single dosage on Day 1.
Dose level (volume)	2000 mg/kg (2.13 mL/kg) body weight. 5000 mg/kg (5.32 mL/kg) body weight. No correction was made for the purity of the test item.

6.7. Observations

Mortality/Viability	Twice daily.
Body weights	Days 1 (pre-administration), 8 and 15.
Clinical signs	At periodic intervals on the day of dosing (Day 1) and once daily thereafter, until Day 15. The signs were graded according to fixed scales and the time of onset, degree and duration were recorded: Maximum grade 4: grading slight (1) to very severe (4) Maximum grade 3: grading slight (1) to severe (3) Maximum grade 1: presence is scored (1).
Necropsy	At the end of the observation period, all animals were sacrificed by oxygen/carbon dioxide procedure and subjected to necropsy. Descriptions of all internal macroscopic abnormalities were recorded.

6.8. Interpretation

The oral LD50 value of the test item was ranked within the following ranges: 0-5, 5-50, 50-300, 300-2000 or 2000-5000 mg/kg b.w. or as exceeding 5000 mg/kg b.w. The LD50 cut-off value was established based on OECD guideline 423. No statistical analysis was performed (The method used is not intended to allow the calculation of a precise LD50 value).

The results were evaluated according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) of the United Nations (including all amendments) and Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of items and mixtures (including all amendments).

6.9. List of Deviations

6.9.1. List of Study Plan Deviations

1. Temporary deviations from the minimum level of daily mean relative humidity occurred.
Evaluation: Laboratory historical data do not indicate an effect of the deviations.
2. No clinical observation was performed for the second group of two animals dosed at 5000 mg/kg.
Evaluation: Sufficient data was available to warrant the study integrity.

The study integrity was not adversely affected by the deviations.

6.9.2. List of Standard Operating Procedures Deviations

Any deviations from standard operating procedures were evaluated and filed in the study file. There were no deviations from standard operating procedures that affected the integrity of the study.

7. ELECTRONIC SYSTEMS FOR DATA ACQUISITION

The following electronic systems were used for data acquisition: REES Centron Environmental Monitoring system version SQL 2.0 (REES scientific, Trenton, NJ, USA); TOXDATA version 8.0 (Charles River Den Bosch, 's-Hertogenbosch, The Netherlands): Clinical signs, Body weights.

8. RESULTS

For detailed results see [APPENDIX 1: TABLES](#).

8.1. Mortality

No mortality occurred at 2000 and 5000 mg/kg body weight.

8.2. Clinical Signs

Hunched posture was seen for all animals on Day 1 and for one animal dosed at 2000 mg/kg on Days 2 and 3 also. Piloerection was seen for the majority of animals on Day 1. Two females dosed at 5000 mg/kg showed abnormal licking on Day 2.

8.3. Body Weights

The body weight gain shown by the animals over the study period was considered to be similar to that expected for normal untreated animals of the same age and strain.

8.4. Macroscopic Findings

Isolated reddish foci on the thymus were found at macroscopic post mortem examination of one female dosed at 2000 mg/kg. Macroscopic post mortem examination of the other animals at termination did not reveal any abnormalities.

Incidental findings included an accessory lobe to the right median lobe of the liver for one female dosed at 2000 mg/kg. This finding is occasionally seen among rats of this age and strain and was therefore considered not related to treatment.

9. CONCLUSION

The oral LD50 value of MLA-3202 in Wistar rats was established to exceed 5000 mg/kg body weight.

According to the OECD 423 test guideline, the LD50 cut-off value was considered to exceed 5000 mg/kg body weight.

Based on these results, MLA-3202 is not classified and has no obligatory labelling requirement for acute oral toxicity according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) of the United Nations (2015) (including all amendments) and Regulation (EC) No 1272/2008 on classification, labelling and packaging of items and mixtures (including all amendments).

APPENDIX 1: TABLES

Table 1 Mortality data

TEST DAY	1	1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
HOURS AFTER TREATMENT	0	2	4														
FEMALES 2000 MG/KG	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
FEMALES 2000 MG/KG	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
FEMALES 5000 MG/KG	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
FEMALES 5000 MG/KG	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Table 2 Clinical signs

TEST DAY		1	1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
HOURS AFTER TREATMENT	MAX GRADE	0	2	4														
FEMALES 2000 MG/KG																		
ANIMAL 1																		
Posture																		
Hunched posture	(1)		1	1	1	-	-	-	-	-	-	-	-	-	-	-	-	-
Skin / fur																		
Piloerection	(1)		-	1	1	-	-	-	-	-	-	-	-	-	-	-	-	-
ANIMAL 2																		
Posture																		
Hunched posture	(1)		1	1	1	-	-	-	-	-	-	-	-	-	-	-	-	-
Skin / fur																		
Piloerection	(1)		-	1	1	-	-	-	-	-	-	-	-	-	-	-	-	-
ANIMAL 3																		
Posture																		
Hunched posture	(1)		1	1	1	1	1	-	-	-	-	-	-	-	-	-	-	-
Skin / fur																		
Piloerection	(1)		-	1	1	-	-	-	-	-	-	-	-	-	-	-	-	-
FEMALES 2000 MG/KG																		
ANIMAL 4																		
Posture																		
Hunched posture	(1)		1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ANIMAL 5																		
Posture																		
Hunched posture	(1)		1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ANIMAL 6																		
Posture																		
Hunched posture	(1)		1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
FEMALES 5000 MG/KG																		
ANIMAL 7																		
Posture																		
Hunched posture	(1)		-	1	1	-	-	-	-	-	-	-	-	-	-	-	-	-
Skin / fur																		
Piloerection	(1)		-	1	1	-	-	-	-	-	-	-	-	-	-	-	-	-
FEMALES 5000 MG/KG																		
ANIMAL 8																		
Behavior																		
Abnormal licking	(1)		-	-	-	1	.	-	-	-	-	-	-	-	-	-	-	-
Posture																		
Hunched posture	(1)		-	1	-	-	.	-	-	-	-	-	-	-	-	-	-	-
Skin / fur																		
Piloerection	(1)		-	1	-	-	.	-	-	-	-	-	-	-	-	-	-	-
ANIMAL 9																		
Behavior																		
Abnormal licking	(1)		-	-	-	1	.	-	-	-	-	-	-	-	-	-	-	-
Posture																		
Hunched posture	(1)		-	1	-	-	.	-	-	-	-	-	-	-	-	-	-	-
Skin / fur																		
Piloerection	(1)		-	1	-	-	.	-	-	-	-	-	-	-	-	-	-	-

. Observation not performed. Sufficient data was available to warrant the study integrity.

Table 3 Body Weights

SEX/DOSE LEVEL	ANIMAL	DAY 1	DAY 8	DAY 15
FEMALES 2000 MG/KG	1	150	171	193
	2	164	202	211
	3	165	191	208
	MEAN	160	188	204
	ST.DEV.	8	16	10
	N	3	3	3
FEMALES 2000 MG/KG	4	158	182	192
	5	167	197	206
	6	178	206	216
	MEAN	168	195	205
	ST.DEV.	10	12	12
	N	3	3	3
FEMALES 5000 MG/KG	7	167	199	207
	MEAN	167	199	207
	ST.DEV.	---	---	---
	N	1	1	1
FEMALES 5000 MG/KG	8	174	195	200
	9	171	190	203
	MEAN	173	193	202
	ST.DEV.	2	4	2
	N	2	2	2

Table 4 Macroscopic findings

ANIMAL	ORGAN	FINDING	DAY OF DEATH
FEMALES 2000 MG/KG			
1		No findings noted	Scheduled necropsy Day 15 after treatment
2		No findings noted	Scheduled necropsy Day 15 after treatment
3	Liver	Right medial lobe: accessory liver.	Scheduled necropsy Day 15 after treatment
FEMALES 2000 MG/KG			
4	Thymus	Focus/foci, isolated, reddish.	Scheduled necropsy Day 15 after treatment
5		No findings noted	Scheduled necropsy Day 15 after treatment
6		No findings noted	Scheduled necropsy Day 15 after treatment
FEMALES 5000 MG/KG			
7		No findings noted	Scheduled necropsy Day 15 after treatment
FEMALES 5000 MG/KG			
8		No findings noted	Scheduled necropsy Day 15 after treatment
9		No findings noted	Scheduled necropsy Day 15 after treatment

APPENDIX 2: TEST ITEM CERTIFICATE OF ANALYSIS



Chemtura Corporation
12 Spencer St
Naugatuck, CT 06770

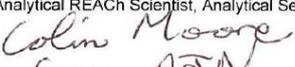
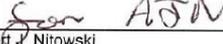
Analytical Services
www.chemtura.com

Certificate of Purity

Customer: Support for Toxicology Studies
 Test Substance Name: MLA3202; Amides, tallow, N,N-bis(2-hydroxypropyl)
 Physical Appearance: Liquid
 CAS No.: 1454803-04-3
 Ref. or Lot Number: RC-1045
 Date of Analysis: revised March 18, 2016 (original issue March 7, 2016)

Percent Composition	Monoisotopic Mass (daltons)	Formula	Structure/ Identity
33.1	397.4	C ₂₄ H ₄₇ NO ₃	C18:1 (oleic) tallow amides, N,N-bis(2-hydroxypropyl)
22.9	371.3	C ₂₂ H ₄₅ NO ₃	C16:0 (palmitic) tallow amides, N,N-bis(2-hydroxypropyl)
13.6	395.4	C ₂₄ H ₄₅ NO ₃	C18:2 (linoleic) tallow amides, N,N-bis(2-hydroxypropyl)
11.0	399.4	C ₂₄ H ₄₉ NO ₃	C18:0 (stearic) tallow amides, N,N-bis(2-hydroxypropyl)
6.0	369.3	C ₂₂ H ₄₃ NO ₃	C16:1 (palmitoleic) tallow amides, N,N-bis(2-hydroxypropyl)
3.2	419.3	C ₂₆ H ₄₅ NO ₃	C20:4 (eicosatetraenoic) tallow amides, N,N-bis(2-hydroxypropyl)
2.0	393.3	C ₂₄ H ₄₃ NO ₃	C18:3 (linolenic) tallow amides, N,N-bis(2-hydroxypropyl)
1.5	282.3	C ₁₈ H ₃₄ O ₂	C18:1 (oleic) acid
1.1	421.4	C ₂₆ H ₄₇ NO ₃	C20:3 (eicosatrienoic) tallow amides, N,N-bis(2-hydroxypropyl)
5.6			Sum of residual components (< 1% each)
100.0			Total


 Blake Lewis
 Analytical REACH Scientist, Analytical Services
 Date 3/7/16



 Albert J. Nitowski
 Sr. Technology Manager
 Analytical and Lab Support Services
 Date 3/7/16

**APPENDIX 3: ENDORSEMENT OF COMPLIANCE WITH THE OECD
PRINCIPLES OF GLP**



ENDORSEMENT OF COMPLIANCE

WITH THE OECD PRINCIPLES OF GOOD LABORATORY PRACTICE

Pursuant to the Netherlands GLP Compliance Monitoring Programme and according to Directive 2004/9/EC the conformity with the OECD Principles of GLP was assessed on 7 – 11, 14 and 16 September 2015 at

WIL Research Europe B.V.
Hambakenwetering 7
5231 DD 's Hertogenbosch

It is herewith confirmed that the afore-mentioned test facility is currently operating in compliance with the OECD Principles of Good Laboratory Practice in the following area of expertise: physical-chemical testing, toxicity studies, mutagenicity studies, environmental toxicity studies on aquatic and terrestrial organisms, studies on behaviour in water, soil, and air, bioaccumulation, residue studies, analytical and clinical chemistry testing, kinetic and metabolism studies and safety pharmacology.

Utrecht, 3 November 2015

Dr R.M.A. Jaspers
Coordinating/specialist senior inspector

Health Care Inspectorate of the Ministry of Health, Welfare and Sport
Stadsplateau 1, 3521 AZ Utrecht
P.O. Box 2680, 3500 GR Utrecht, The Netherlands